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Semi-Annual Progress Report

Title of Project: The Synthesis of Peptides

Period Covered: July 1, 1952 - December 31, 1952

Date of Submission: December 30, 1952

Principal Investigator: Joseph S. Fruton

Contractor: Yale University

Subtask No: NR 124-051 Contract No: Nonr 262(00)

As indicated in my previous Semi-Annual report, work on this project was to be resumed on August 1, 1952 since we had succeeded in securing the services of Dr. Louis A. Cohen. Funds are currently available for the support of Dr. Cohen's work until March 31, 1953. An application for the renewal of the grant until June 30, 1954 was submitted on March 31, 1952.

During the past five months, Dr. Cohen and I have conducted work on (1) the synthesis of peptides containing serine and phosphoserine residues; (2) the use of trifluoroacetic anhydride in peptide synthesis; (3) the use of amino acid thiol esters in peptide synthesis.

Peptides of Serine and Phosphoserine - Attention was first directed to the development of a satisfactory method for the synthesis of phospho-L-serine, since the procedures in the literature leave much to be desired. Attempts to obtain this material by treatment of the copper complex of serine with $POCl_3$ or diphenylphosphoryl chloride (followed by hydrogenolysis) were unsuccessful, possibly because the copper chelate involves the serine hydroxyl group. For this reason, emphasis is now being placed on the

phosphorylation of carbobenzoxy-L-serine benzyl ester, which has been obtained for the first time by the carbobenzoxylation of L-serine benzyl ester. Of a number of methods tested, the best procedure for the preparation of the last named compound involves the use of benzyl alcohol - hydrogen chloride.

Preliminary experiments have been performed on the synthesis of serine peptides in which hydroxyl group of serine is involved in an ester linkage with the carboxyl group of another amino acid. For this work, the carbobenzoxy-L-serine benzyl ester is a valuable starting material, since it can be treated with the acid chloride of a carbobenzoxyamino acid to give a coupling product that should yield the desired O-peptide on hydrogenolysis. Some difficulty has been encountered in performing the coupling reaction to give a pure product, and further work is necessary.

The synthesis of peptides of L-serine has been improved by modification of the procedures described in the literature. It is planned to subject compounds such as carbobenzoxy-L-seryl-L-alanine benzyl ester to phosphorylation with dibenzylphosphoryl chloride and to obtain the phosphoserine peptides by hydrogenolysis of the coupling product.

Development of New Reagents for Peptide Synthesis - Experiments were conducted to examine the possible usefulness of trifluoroacetic acid anhydride for the synthesis of peptides. Thus, carbobenzoxyglycine and the anhydride were allowed to react, and the mixed anhydride treated with an amino acid ester. However, under the conditions employed, the yields of desired product were inferior to those obtained by older methods. It may

be that with other acylamino acids, the reaction with trifluoroacetic anhydride may be more satisfactory; such experiments are planned.

The use of thiol esters of acylamino acids for peptide synthesis has recently been reported in the literature. Although we performed preliminary experiments along this line prior to the appearance of this report, our efforts in this direction have been suspended so as not to duplicate studies known to be conducted elsewhere.

Respectfully submitted,

Joseph S. Fruton

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